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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/072,047	02/08/2002	David R. Cox	UCSF-127CON	3618

24353 7590 08/28/2003

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EXAMINER
FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 08/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/072,047	COX ET AL.	
	Examin r	Art Unit	
	Jeffrey Fredman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *17 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-52* is/are pending in the application.

4a) Of the above claim(s) *51 and 52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 27-50 in the paper filed June 17, 2003, is acknowledged.

Double Patenting

2. Claims 27-50 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,406,847. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-12 of U.S. Patent No. 6,406,847 represent a species within the genus of the current claims. Such a species anticipates, and necessarily renders obvious, the broader generic claims of the current application.

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim Rejections - 35 USC § 112

4. Claims 27-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for markers with mismatches of at least 5 nucleotides

where the second mismatch is four nucleotides or less, does not reasonably provide enablement for markers of four or less mismatched nucleotides where the second mismatch is four nucleotides or less. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method of detecting mismatches by the use of in vivo mismatch repair where a second marker sequence with a mismatch is also present in a multiplex assay. The invention is in an class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The invention is a method of mismatch detection in which a mismatch between two DNA strands of interest is detected by corepair of the mismatch of interest and a mismatch of at least about 5 nucleotides in a detectable marker. The claims are broadly

drawn to mismatches of any length (except for claim 39 where the mismatch is a single nucleotide polymorphism) and where the detectable marker mismatch can also be of any length.

Quantity of Experimenation

The quantity of experimentation in this area is extremely large since there is significant variability in the activity of mismatch repair systems. Since the only mismatch repair system used requires at least 5 nucleotides in the marker sequence and less than 5 nucleotides in the corepair mismatch segment, performance of the method as current claimed, where these nucleotide requirements are absent, would require identification of a new mismatch repair system in a new organism. Screening for such a new mismatch repair system would require years of inventive effort, with many intervening steps, without any reasonable expectation that there could be effective reduction to practice in finding such a new mismatch repair system and with no guarantee of success in any of the succeeding steps.

The unpredictability of the art and the state of the prior art

The prior art of Parker et al (Proc. Natl. Acad. Sci. (1992) 89:1730-1734) teaches that mismatches of 1-4 nucleotides are repaired while mismatches of 5 nucleotides are not repaired by the E. coli dam directed mismatch system (abstract). Parker further notes that mismatches of 7, 9 and 11 bases are also not repaired by this system (page 1733, last paragraph to page 1734, first paragraph). The claimed method requires that the mutation in the detectable marker be unrepairable without a second mismatch or the method will yield unpredictable results. The results will be unpredictable because the following scenarios may result. In the classic method, a 5 bp mismatch in the

detectable marker and a 1 bp mismatch in the DNAs of interest will yield corepair of both and activation of the marker, while with a 5 bp mismatch in the detectable marker and no mismatch in the DNAs of interest, there will be no activation of the marker. If 3 or 4 bp mismatches are used in the detectable marker and a 1 bp mismatch occurs in the DNAs of interest, there should be corepair to yield activation of the marker. However, in the control situation here, where a 3 or 4 bp mismatch is present in the marker but no mismatch in the DNAs of interest, the E. coli dam directed mismatch system may repair the mismatch and yield activation of the marker. Thus, no information will be conveyed about the state of mismatch of the DNAs of interest because, while a null result will mean no mismatch, a positive result may or may not mean a mismatch is present in the DNAs of interest. The method, using 3 or 4 bp mismatches, will therefore yield an unpredictable result.

Working Examples

There are no working examples of mismatches of less than 5 nucleotides in the specification.

Guidance in the Specification.

The specification provides working examples and guidance for situations in which the mismatch in the marker gene is 5 nucleotides or greater, but provides not teaching or guidance of mismatches less than 5 nucleotides. In fact, the specification clearly states "E. coli detects single point misniatches as well as one-, two-, and three-nucleotide loops, but it does not detect loops of 5 nucleotides or more. (see page 7, lines 10-11 of the specification)."

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability and the teaching against the use of less then 5 nucleotide marker mismatches by the art is opposed to patentability (see Parker). It is therefore concluded that the scope of the invention is limited to at least 5 bp mismatches in the detectable marker since a large amount of experimentation is required due to the breadth of the claim to include less than 5 bp mismatches, and since there is an absence of guidance in the specification, an absence of working examples, as well as negative teachings in the prior art of Parker and the high level of unpredictability balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1634